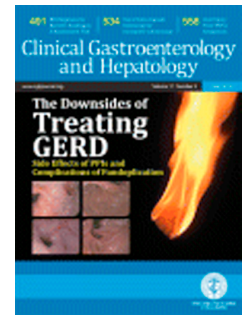


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Efficacy of Mirtazapine in Patients With Functional Dyspepsia and Weight Loss

Short title: Mirtazapine in functional dyspepsia

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Abbreviations: FD = functional dyspepsia
MDP = Minimal distending pressure
5-HT = 5-hydroxytryptamine
DSS = dyspepsia symptom severity

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Background & Aims: A subset of patients with functional dyspepsia (FD) present with early satiation and weight loss, for which there are no established therapeutic options. We investigated the efficacy of mirtazapine (an anti-depressant and antagonist of the histamine receptor H₁, the α_2 adrenergic receptor, and the serotonin receptors 5-HT_{2C} and 5-HT₃) in patients with FD and weight loss.

Methods: We conducted a randomized, placebo-controlled pilot trial studied 34 patients with FD (29 women; mean age, 35.9 \pm 2.3 years) with weight loss >10% of original body weight (mean loss of 12.4 \pm 2.3 kg) without depression or anxiety. After a run-in period, patients were randomly assigned to groups given placebo (n=17) or mirtazapine 15 mg each day for 8 weeks (n=17), in a double-blind manner. Subjects were evaluated during a 2-week baseline and 8-week treatment for dyspepsia symptom severity, quality of life (based on the Nepean Dyspepsia Index), and gastrointestinal-specific anxiety; they were given a nutrient challenge test and weighed. Data were analyzed using linear mixed models followed by planned contrasts with adaptive stepdown Bonferroni multiple testing correction.

Results: Two patients in each group dropped out. At weeks 4 and 8, mirtazapine significantly reduced mean dyspepsia symptom severity scores compared to week 0 ($P=.003$ and $P=.017$, respectively); there was no significant reducing in the placebo group ($P>.37$ for weeks 4 and 8). The difference in change from week 0 between mirtazapine and placebo showed a trend with a large effect size at week 4 ($P=.059$) that was not significant at week 8 ($P=.55$). However, improvements from week 0 to weeks 4 and 8 were significantly larger in the mirtazapine than placebo group for early satiation, quality of life, gastrointestinal-specific anxiety, weight, and nutrient tolerance (mostly with large effect sizes).

Conclusions: In a randomized, placebo-controlled trial, mirtazapine significantly improved early satiation, quality of life, gastrointestinal-specific anxiety, nutrient tolerance, and weight loss in patients with FD. Clinicaltrial.gov number, NCT01240096.

KEY WORDS: stomach, gastric barostat, gastric accommodation, gastric emptying, clinical trial, drug

INTRODUCTION

Functional dyspepsia (FD), defined as the presence of symptoms thought to originate in the gastroduodenal region in the absence of any organic, systemic or metabolic disease that is likely to explain the symptoms, is one of the most common gastrointestinal disorders(1). According to Rome III criteria, early satiation, postprandial fullness, epigastric pain and epigastric burning constitute the typical FD symptoms. Other symptoms like upper abdominal bloating, belching and nausea often co-exist, and a subset of patients may experience weight loss(1,2).

Weight loss is normally considered an alarm symptom(1), but may be present in up to 13% of subjects with dyspeptic symptoms in the general population and up to 40% of tertiary care FD patients(3-6). Weight loss in dyspepsia is associated with symptoms of early satiation and epigastric pain, both in the general population and in tertiary care(3-6). Impairment of gastric accommodation, a relaxation of the proximal stomach that provides the meal with a reservoir enabling a gastric volume increase without a rise in pressure(7), may underlie weight loss in FD (3). Impaired accommodation occurs in 40% of FD patients, and these have more prevalent symptoms of early satiation and weight loss (4). Based on observations in healthy controls and FD patients, restoration of accommodation is a valid therapeutic target to improve early satiation and weight recovery(4,7,8).

At present, there is no efficacious treatment for FD patients with weight loss. Mirtazapine is an antidepressant with H_1 -, α_2 -, $5-HT_{2c}$ - and $5-HT_3$ -receptor antagonistic properties. Its use in depression is associated with weight gain. In part through its $5-HT_3$ -receptor antagonistic action, mirtazapine has nausea-suppressive properties, and anecdotal observations suggest efficacy for mirtazapine in FD, but controlled studies are lacking(9,10).

Our aim was to conduct a randomized, double-blind placebo-controlled mechanistic pilot trial to evaluate the influence of mirtazapine on symptoms, gastric emptying rate, and nutrient tolerance in FD patients with weight loss.

MATERIALS AND METHODS

Patient selection

Patients (aged 20-70 years) with FD according to the Rome III criteria and with weight loss in excess of 10% of their body weight since onset of symptoms were eligible(1). Organic or metabolic disease was excluded by routine biochemistry, upper abdominal ultrasound and upper gastrointestinal endoscopy. During endoscopy, biopsies were taken from antrum and corpus and stained for the presence of *Helicobacter pylori*. Dyspeptic symptoms had to be present at least 3 days per week, with 2 or more symptoms scored as relevant or severe on the symptom questionnaire (see below).

Exclusion criteria were the presence of esophagitis, gastric atrophy or erosive gastroduodenal lesions on endoscopy, heartburn as predominant symptom, a history of peptic ulcer or major abdominal surgery. All drugs potentially affecting gastrointestinal motility or sensitivity (acid-suppressives, prokinetics, drugs affecting gastric acid secretion and analgesics other than paracetamol) were discontinued at least one week prior to the start of the study and were forbidden for the entire course of the study.

Patients with current anxiety or depression based on the HADS questionnaire (see below), with anorexia nervosa or other eating disorders, and patients on antipsychotics or antidepressants during the last 6 weeks were not eligible. Pregnant women or patients of childbearing potential without effective contraception were also excluded.

Informed consent was obtained from each participant and the protocol had been approved by the University Hospital Ethics Committee prior to the start of the study. The study was registered on www.clinicaltrials.gov as NCT01240096.

Study design

The study design is summarized in *Supplementary Figure 1*. Patients underwent a gastric barostat study (details in *Supplement*) prior to a two-week run-in period. At the end of the run-in period and after the treatment period, patients underwent a octanoic acid breath test to quantify solid gastric emptying, a nutrient drink challenge test to quantify nutrient volume tolerance(17-19) (details in *Supplement*) and filled out a dyspepsia symptom severity (DSS) questionnaire previously shown to be reproducible and sensitive to change(12,13) and consisting of 8 dyspeptic symptoms (epigastric pain, postprandial fullness, upper abdominal bloating, early satiation, nausea, vomiting, epigastric burning, belching) during the last two weeks on a Likert scale (absent, mild, moderate, severe). DSS is defined as the sum of all 8 items. In addition, they filled out the Hospital Anxiety Depression Scale (HADS), the Visceral Sensitivity Index (VSI) and the short-form Nepean Dyspepsia Index (SF-NDI)(14-16). The HADS allows to quantify anxiety and depression severity, through 7 questions per subscale(14). The VSI is a 15-item questionnaire for assessment of gastrointestinal-specific anxiety(15). The NDI is a 25-item questionnaire assessing 5 subscales of quality of life impact in FD: tension/sleep, interference, eating/drinking, knowledge/control, and work/study (16). After the 2-week run-in period, patients were randomly assigned to 8 weeks with mirtazapine 15 mg or a matching placebo melting tablet, taken at bedtime. The 15 mg dose was chosen based on tolerability, clinical experience, literature reports, and on the traditional use of lower doses of psychotropic drugs for FGID(1,9,10). Both active drug and matching placebo were supplied by the manufacturer (MSD Belgium, Brussels, Belgium). The questionnaires were filled out again after 4 weeks of the treatment period. To provide details on onset of changes in symptom intensities during treatment, patients also filled out a daily diary indicating severity for the same dyspeptic symptoms on 100mm visual analogue scales.

Statistical analysis

All authors had access to the study data and reviewed and approved the final manuscript. Descriptive data are given as mean \pm SD. All outcomes were analyzed using linear mixed models; estimates are given as mean \pm SEM. Effect sizes are given as Cohen's d. A 2x3 mixed ANOVA model was used with "drug" (mirtazapine,

placebo) as between-subject factor and “week” (0, 4, 8) as within-subject factor. The drug-by-week interaction effect was the effect of primary interest which was followed up by the following planned contrasts, with stepdown Bonferroni multiple testing correction. First, the outcomes were compared between week 0, week 4 and week 8 within each treatment arm separately by paired Student’s t-tests. Second, for each outcome, the change between week 0 on the one hand and week 4 and week 8 on the other hand were compared between treatment arms using independent sample Student’s t-tests.

RESULTS

Patient characteristics

Thirty-four patients (29 women, mean age 35.9 ± 13.5 , BMI 22.1 ± 3.9 kg/m²) were enrolled. They reported FD symptoms since $14(4-222)$ months and had a mean weight loss of 12.4 ± 9.7 kg since the onset of symptoms. An acute symptom onset, suggestive of post-infectious FD, was reported by 65%. According to Rome III criteria, 17 had postprandial distress syndrome (PDS), 9 epigastric pain syndrome (EPS) and 8 both EPS and PDS.

Table 1 summarizes the symptom pattern at the end of the run-in period. All patients were *Helicobacter pylori* negative and none had a previous history of eradication; 15% had delayed gastric emptying for solids ($t^{1/2}$ range 111-134 min), one patient had rapid emptying ($t^{1/2}$ 27 mins), 50% had impaired gastric accommodation and 44% were hypersensitive to gastric balloon distention. At baseline, anxiety and depression levels, as assessed by the HADS questionnaire, were 6.4 ± 4.6 and 5.0 ± 3.6 respectively. Seventeen FD patients were randomized to active drug and 17 to placebo. These groups did not differ in demographics, symptom pattern and anxiety and depression rates at randomisation (*Table 2*).

Conduct of the study and adverse events

No serious adverse events occurred. During the double-blind phase, a total of 4 patients dropped out: two in the placebo arm because of lack of therapeutic effect and 2 in the mirtazapine arm because of adverse events of fatigue and sleepiness.

Dyspepsia symptom severity

The drug-by-week interaction showed a trend [$F(2,59)=2.63$, $p=0.08$]. Planned contrasts revealed a significant difference between week 0 (10.9 ± 0.9) and week 4 (7.9 ± 1.3) as well as week 8 (8.6 ± 1.4) for mirtazapine ($p=0.003$ and $p=0.017$,

respectively). For placebo, there were no significant differences between week 0 (11.4 ± 0.9) and week 4 (11.1 ± 1.2) or week 8 (10.4 ± 1.0) ($p=0.38$ and $p=0.72$, respectively). The difference in change from week 0 between mirtazapine and placebo showed a trend at week 4 (-3.0 ± 0.9 versus -0.3 ± 0.8 , $p=0.059$, $d=0.82$) but not at week 8 (-2.6 ± 0.9 versus -1.0 ± 0.8 , $p=0.55$, $d=0.48$) (*Figure 1A*). Results of per protocol analysis are given in *Supplement*.

For early satiation, where the drug-by-week interaction was significant [$F(2,59)=6.96$, $p=0.002$]. Planned contrasts revealed a significant difference between week 0 (1.88 ± 0.21) and week 4 (1.06 ± 0.25) as well as week 8 (1.11 ± 0.24) for mirtazapine ($p=0.002$ and $p=0.0003$, respectively). For placebo, there were no significant differences between week 0 (1.53 ± 0.19) and week 4 (1.47 ± 0.17) or week 8 (1.77 ± 0.22) ($p=0.71$ and $p=0.56$, respectively). The difference in change from week 0 between mirtazapine and placebo was significant at week 4 (-0.82 ± 0.24 versus -0.06 ± 0.16 , $p=0.019$, $d=0.96$) and at week 8 (-0.77 ± 0.19 versus -0.24 ± 0.22 , $p=0.002$, $d=0.67$) (*Figure 1B*). No significant effects were found for the other three cardinal FD symptoms. For nausea, the drug-by-week interaction effect was not significant [$F(2,32)=2.03$, $p=0.15$], but planned contrasts revealed a trend for the difference between week 0 (1.53 ± 0.24) and week 4 (1.02 ± 0.25) as well as week 8 (1.09 ± 0.26) for mirtazapine ($p=0.074$ and $p=0.096$, respectively). The supplementary file provides information on symptom evaluation with daily diaries.

Weight

The drug-by-week interaction was significant [$F(2,58)=12.82$, $p<0.0001$]. Planned contrasts revealed that during placebo treatment, no significant change in body weight occurred compared to week 0 (59.0 ± 2.7) at either week 4 (59.1 ± 2.7 , $p=1.0$) or week 8 (58.8 ± 2.6 , $p=1.0$). Mirtazapine treatment, on the contrary, was associated with significant weight gain compared to week 0 (67.0 ± 3.5) at both week 4 (69.5 ± 3.5 , $p=0.0008$) and week 8 (70.9 ± 3.7 , $p<0.0001$). The difference in weight change from week 0 between mirtazapine and placebo was significant at week 4 (2.5 ± 0.6 versus 0.1 ± 0.3 , $p=0.003$, $d=1.40$) and week 8 (3.9 ± 0.7 versus -0.2 ± 0.4 , $p<0.0001$, $d=1.86$) (*Figure 2A*). In terms of percentage of original body weight, the differences were -

0.2±2.2 and 6.4±4.6% respectively ($p<0.0001$).

Nutrient tolerance

At baseline, nutrient tolerance was below the lower normal range of 979 kcal in 91% of the patients (16). The drug-by-week interaction was significant [$F(1,26)=8.24$, $p=0.008$]. Planned contrasts showed that after placebo treatment, no significant change in nutrient tolerance occurred at week 8 (638.3±77.7 kcal) compared to week 0 (668.4±75.0 kcal) ($p=0.44$). After mirtazapine treatment, nutrient tolerance was significantly improved at week 8 (704.2±67.5 kcal) compared to week 0 (542.7±42.3 kcal) ($p=0.007$). The change between week 8 and week 0 was significantly different between mirtazapine and placebo (+161.5±54.9 kcal versus -30.1±37.9 kcal, $p=0.008$, $d=1.05$) (*Figure 2B*). The change in nutrient volume tolerance was not correlated to baseline weight or BMI, or to the weight loss prior to therapy and the weight gain during therapy.

Gastric emptying

The drug-by-week interaction was not significant [$F(1,30)=2.46$, $p=0.13$]. In planned contrasts, no significant differences were found either within treatment arms [week 0 versus week 8: 79.1±7.0 versus 85.8±8.6 ($p=0.15$) for placebo; 88.5±7.0 versus 77.0±7.8 ($p=0.45$) for mirtazapine] or for the difference week 8 - week 0 between mirtazapine and placebo (-11.5±7.7 versus +6.7±8.6 minutes, $p=0.13$, $d=0.57$).

Questionnaires

Quality of life (SF-NDI)

A significant drug-by-week interaction effect was found [$F(2,32)=4.61$, $p=0.018$]. In the mirtazapine arm, scores decreased significantly from week 0 (31.7±2.1) to week 4 (25.1±2.5, $p=0.001$) and week 8 (24.6±2.7, $p=0.001$). In the placebo arm, no significant changes were found from week 0 (30.9±2.1) to week 4 (29.5±2.5, $p=0.83$)

nor to week 8 (30.8 ± 2.7 , $p=0.95$). The change from week 0 was significantly different between mirtazapine (-7.1 ± 1.8) and placebo (0.1 ± 1.8) at week 8 ($p=0.033$, $d=1.03$), with a trend with large effect size ($p=0.092$, $d=0.84$) at week 4 (-6.6 ± 1.6 and 1.4 ± 1.6 for mirtazapine and placebo, respectively). The results for the 5 NDI subscales are summarized in *Table 3*. Significant drug-by-week interaction effects as well as significant between-treatment differences for the change from week 0 to week 8 were found for eating/drinking and work/study.

Anxiety and depression (HADS)

Anxiety and depression scores were not significantly altered by 8 weeks of placebo treatment, but mirtazapine treatment was associated with a small but statistically significant improvement of anxiety at week 8 compared to week 0 (*Table 3*). No significant between-treatment differences were found. Changes in depression or anxiety scores were not correlated to changes in symptom scores and did not predict treatment responses.

Gastrointestinal-specific anxiety (VSI)

A significant drug-by-week interaction effect was found [$F(2,31)=6.7$, $p=0.004$]. This was driven by the fact that mirtazapine significantly improved VSI ratings, with no significant change under placebo treatment, resulting in a significant difference for the change from baseline at week 4 (-11.5 ± 3.2 versus $+1.3 \pm 2.3$, $p=0.003$, $d=1.19$) which was maintained at week 8 (-11.3 ± 4.1 versus $+0.4 \pm 2.9$, $p=0.03$, $d=0.85$) (*Table 3*). Changes in VSI were not correlated to symptom improvement or weight recovery.

DISCUSSION

FD is a highly prevalent condition, with no established efficacious therapy. Current approaches focus on acid suppressive or prokinetic drugs, but symptomatic benefit is insufficient in many patients(1,2,24,25). In the subgroup of FD patients with unintentional weight loss, the lack of efficacious treatment options is even more troubling. In this pilot study in FD with weight loss, mirtazapine 15 mg in the evening improved early satiation scores and nutrient tolerance compared to placebo. A trend (with large effect size) was found for overall dyspepsia symptom score at week 4, but not week 8. This was associated with significant recovery of weight loss and improvement of quality of life and visceral specific anxiety scores.

The symptomatic benefit of mirtazapine was most consistent across questionnaire and diaries for the symptom of early satiation (DSS, diaries), and to a lesser extent for nausea (diaries, trend in DSS). Symptoms of epigastric pain and burning were not affected, suggesting that mirtazapine treatment may be most beneficial for the PDS subgroup(1), although the study was not powered for subgroup analysis. Based on the diaries, symptomatic benefit seems to occur from week 3 onwards. Early satiation responds best to mirtazapine, suggesting that the drug specifically affects the mechanism underlying this symptom (accommodation and its signalling to the brain). Nausea only significantly improved after mirtazapine in the diary assessment, where improvement, albeit to a lesser extent, also occurred with placebo, without significant differences between both arms. This probably reflects the limited sample size of this mechanistic pilot trial, and the possibility that the 100 mm VAS is more sensitive to small changes than the 4-level DSS severity scale.

Based on its pharmacological profile, mirtazapine may improve FD symptoms through a number of mechanisms. The drug is used for treating depression and anxiety. Anxiety or depression co-morbidity in FD is high(26), and in healthy volunteers, experimentally induced anxiety is associated with impaired accommodation to a meal and decreased nutrient tolerance(27). In hypersensitive FD patients, state anxiety is significantly correlated with lower discomfort and pain thresholds, and decreased compliance during gastric balloon distention(28). However, patients in the present study were selected for absence of anxiety and

depression co-morbidity and symptom improvement was not correlated to changes in anxiety and depression. Mirtazapine treatment was associated with significant improvement of gastrointestinal-specific anxiety(29). In a previous study, we found a significant negative correlation between VSI scores and impairment of duodenal mucosal integrity in FD(30). It is unclear whether improvement in gastrointestinal-specific anxiety with mirtazapine occurs secondarily to improvement of FD symptoms and weight recovery, or whether mirtazapine directly affects its putative central mechanisms. The lack of correlation with symptom improvement would argue against the former mechanism. Based on this finding, it is conceivable that the drug might be effective in other functional disorders with high gastrointestinal-specific anxiety such as IBS.

The symptoms that most consistently improved during mirtazapine treatment are early satiation and weight loss. In several pathophysiological and mechanistic studies, impaired gastric accommodation has been associated with early satiation and weight loss(2,4,7,8,19,31). The prevalence of impaired accommodation in the current patient group was 50% at baseline, but the protocol did not include a repeat gastric barostat assessment during treatment. Previously, we proposed the satiety drinking test as a surrogate marker for gastric accommodation(19). Using this test, nutrient volume tolerance was significantly increased by mirtazapine, but not placebo. These findings argue in favor of enhanced gastric accommodation by mirtazapine. However, a central mechanism involving increased appetite through 5-HT_{2C} receptor antagonism can also be involved(32). Hence, further specific mechanistic studies are needed to confirm whether or not mirtazapine enhances gastric accommodation in man. If the effect of mirtazapine on nutrient tolerance and body weight does not involve enhanced accommodation, but rather reflects a central effect, the drug may also be effective in the treatment of other functional disorders with weight loss, where impaired accommodation is not the underlying mechanism.

The present study has a number of limitations. Due to the setting and nature of this pilot trial, we enrolled only tertiary care patients and the sample size is limited. Hence, findings are not necessarily applicable to non-tertiary care FD. Furthermore, due to the small sample size, baseline measurements were not always similar, although no significant differences between both groups were found. However, the latter issue was handled by using linear mixed models and planned contrasts to

compare the change from baseline between treatment arms. Finally, the sample size precludes separate analysis in PDS and EPS patients.

To date, enhanced accommodation in FD has been observed with tegaserod, buspirone and acotiamide(33-36), but whether these drugs allow recovery of weight loss in FD has not been addressed (19,35,39). Mirtazapine was acceptably well tolerated in the present study, but two out of seventeen patients discontinued the drug for drowsiness, a well-known adverse event with mirtazapine use(40). Hence, the present pilot study shows that mirtazapine has the potential to become the treatment of choice for FD patients with weight loss, and evaluation in larger multi-center studies is warranted.

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TABLES

Table 1. Symptom profile in the patient population at the end of the run-in period (n=34).

Rows indicate the number of patients for each symptom severity level.

Symptom	Absent	Mild	Moderate	Severe
Postprandial fullness	0	8	22	4
Upper abdominal bloating	0	8	21	5
Early satiation	4	6	20	4
Epigastric pain	4	11	14	5
Nausea	6	9	14	5
Belching	10	12	9	3
Epigastric burning	14	12	6	2
Vomiting	24	6	1	3

Table 2. Characteristics of the patients in both groups.

Variable	Placebo group	Mirtazapine group	p
Age (years)	39.9±3.5	31.8±2.7	NS
Sex (f/m)	15/2	14/3	NS
BMI (kg/m ²)	20.8±1.0	24.1±1.2	NS
Weight loss (kg)	11.1±2.5	14.4±4.5	NS
DSS	11.4±0.9	10.9±0.9	NS
Minimal distending pressure (MDP) (mm Hg)	6.7±0.3	7.5±0.3	NS
Fasting discomfort threshold (mm Hg above MDP)	9.3±1.1	8.3±0.9	NS
Gastric compliance (ml/mm Hg)	74±8	62±15	NS
Gastric accommodation (ml)	80±36	64±29	NS
HAD anxiety	7.5±1.3	5.2±0.7	NS
HAD depression	4.8±0.7	5.1±1.2	NS
VSI	29.4±4.9	33.7±3.5	NS

Table 3. Influence of 8 weeks of treatment with placebo or mirtazapine on SF-NDI subscales, HADS and VSI.

* $p < 0.05$, *** $p < 0.001$ compared to week 0 within the mirtazapine treatment arm. Bold indicates significant drug-by-week interaction effect and significant between-group difference for the change from week 0 to week 8.

(sub)scale	baseline mirtazapine	8 weeks mirtazapine	baseline placebo	8 weeks placebo
<i>Short-form Nepean Dyspepsia Index</i>				
Tension	4.8±0.6	4.0±0.6	6.1±0.6	5.7±0.6
Interference with daily activities	6.9±0.7	5.0±0.8*	6.3±0.7	5.9±0.8
Eating/drinking	8.0±0.5	5.8±0.6***	7.6±0.5	7.3±0.6
Knowledge/control	3.9±0.3	3.4±0.3	4.8±0.5	4.2±0.5
Work/study	8.1±0.8	6.4±1.0*	6.1±0.8	7.6±1.0
<i>Hospital Anxiety and Depression Scale</i>				
Anxiety	5.2±0.7	3.9±0.8*	7.5±1.3	4.1±0.8
Depression	5.1±1.2	3.9±1.2	4.8±0.7	4.9±1.1
<i>Visceral Sensitivity Index</i>				
VSI	33.7±4.2	22.8±4.2***	31.2±4.3	31.6±4.3

FIGURES**Figure 1.**

A. Change in Dyspepsia Symptom Severity Score after 8 weeks of mirtazapine or placebo.

B. Individual line plots of changes in severity ratings of early satiety.

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared to baseline within the mirtazapine arm.

[†] $p < 0.05$, ^{††} $p < 0.01$ change from baseline between treatments.

Figure 2.

A. Change in body weight after 4 and 8 weeks of treatment with placebo or mirtazapine.

B. Change in meal volume tolerance during a nutrient challenge test after 8 weeks treatment with placebo or mirtazapine treatment.

** $p < 0.01$, *** $p < 0.001$ compared to baseline within the mirtazapine arm. ^{††} $p < 0.01$,

^{†††} $p < 0.001$ change from baseline between treatments.

Supplementary Figure 1. Schematic study outline.**Supplementary Figure 2. Influence of 8 weeks placebo treatment on daily diary ratings of dyspeptic symptoms.**

A. Early satiation

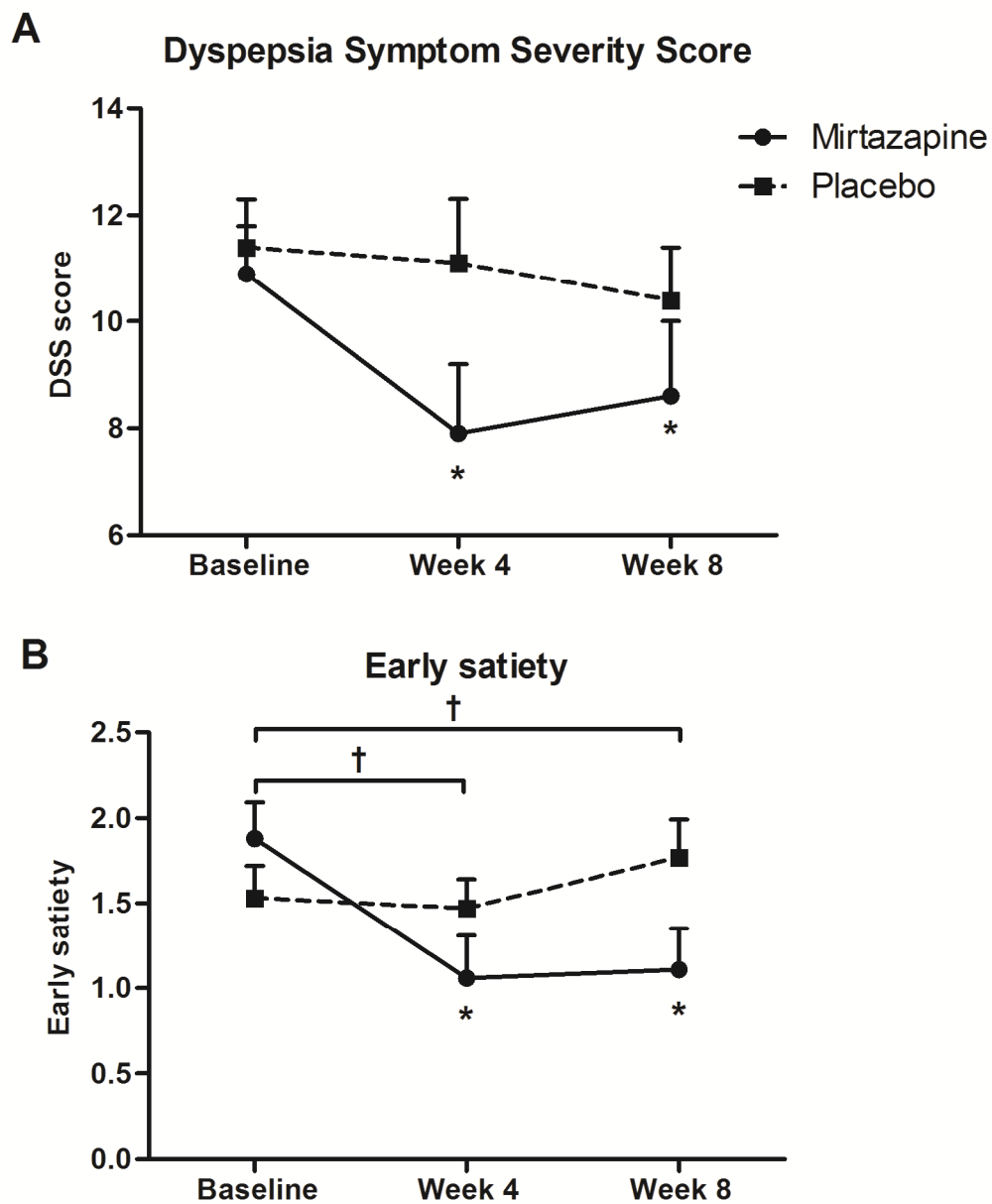
B. Postprandial fullness

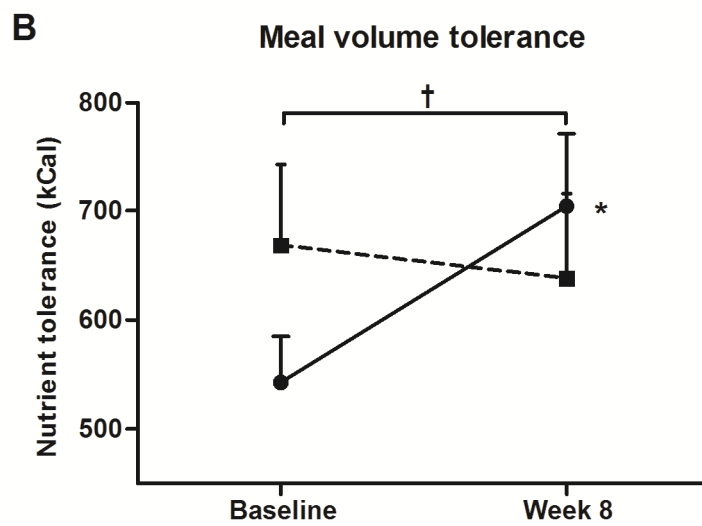
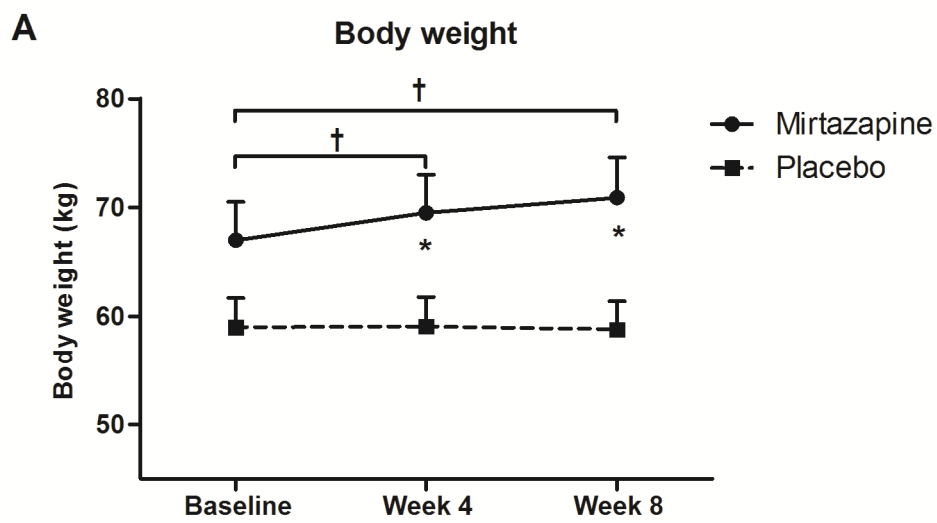
C. Epigastric pain

D. Nausea

* $p < 0.05$, ** $p < 0.01$ compared to baseline within the mirtazapine arm. [#] $p < 0.05$,

^{##} $p < 0.01$ compared to baseline within the placebo arm.



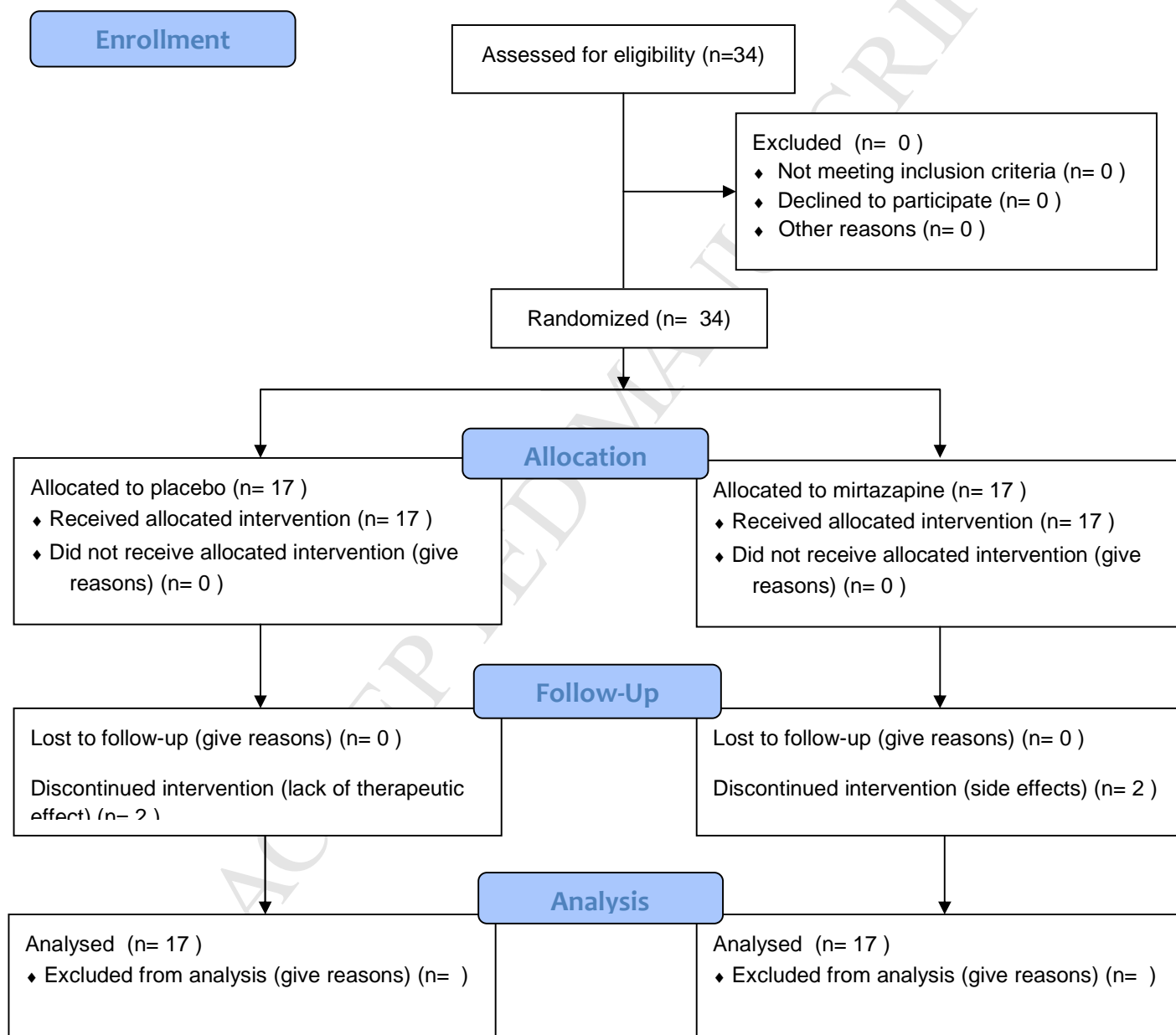




CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram



METHODS

Gastric emptying breath test

Gastric emptying rates for solids and liquids were determined using the ^{14}C -octanoic acid and ^{13}C -glycin breath test respectively (17,18). In the treatment phases of the study, study medication was ingested 15 minutes prior to the meal. The test meal consisted of 60 g of white bread, an egg, the yolk of which was doped with 74 kBq of ^{14}C -octanoic acid sodium salt (DuPont, NEN Research, Boston, MA, USA) and 300 ml of water in which 100 mg ^{13}C -glycin (99% enrichment; Isotec, Miamisburg, OH, USA) was dissolved. All meals were consumed within a 5 minute period. The total caloric value of the test meal was 250 kcal. Breath samples were taken before the meal and at 15-minute intervals for a period of 240 minutes postprandially. At each sampling point, the subject exhaled into two different containers for measuring exhaled ^{13}C and ^{14}C respectively. The radiation in the container containing the ^{14}C sample was determined by liquid scintillation counting while the ^{13}C breath content was determined by on-line gas chromatographic purification-isotope ratio mass spectrometry as described before (17,18).

Satiety drink test

A peristaltic pump (Minipuls2, Gilson, Villiers-Le-Bel, France) dispensed a liquid meal (Nutridrink, Nutricia, Belgium) in one of two beakers at a rate of 15ml/min. Patients were requested to maintain intake of the liquid meal at a rate equal to the dispensing rate, thereby alternating the beakers as they are filled and emptied. At 5-minute intervals, they scored their satiety and other epigastric sensations using a graphic rating scale that combines verbal descriptors on a scale graded from 0 to 5 (1=threshold, 5=maximum satiety). Patients were instructed to cease the meal intake when a score of 5 was reached (4,19).

Gastric barostat study

Following an overnight fast of at least 12 hours, a double lumen polyvinyl tube (Salem sump tube 14 Ch., Sherwood Medical, Petit Rechain, Belgium) with an adherent plastic bag (1200 ml capacity; 17 cm maximal diameter) finely folded, was introduced through the mouth and secured to the subject's chin with adhesive tape. The position of the bag in the gastric fundus was checked fluoroscopically. The polyvinyl tube was then connected to a programmable barostat device (Synectics Visceral Stimulator, Stockholm, Sweden). To unfold the bag, it was inflated with a fixed-volume of 300 ml of air for two minutes with the study subject in a recumbent position, and again deflated completely. The subjects were then positioned in a comfortable sitting position with the knees bent (80°) and the trunk up right in a specifically designed bed.

After a 30 minute adaptation period, minimal distending pressure (MDP) was first determined by increasing intrabag pressure by 1 mm Hg every 3 minutes until a volume of 30 ml or more was reached. Subsequently, isobaric distentions were performed in stepwise increments of 2 mm Hg starting from MDP, each lasting for 2 minutes, while the corresponding intragastric volume was recorded. Subjects were instructed to score their perception of upper abdominal sensations at the end of every distending step, using a graphic rating scale that combined verbal descriptors on a scale graded 0-6 (4,5). The endpoint of each sequence of distentions was established at an intrabag volume of 1000 ml, or when the subjects reported discomfort or pain (score 5 or 6). After a 30 minute adaptation period with the bag completely deflated, the pressure level was set at MDP+2 mm Hg during at least 90 minutes. In the treatment phases of the study, study medication was ingested after 15 minutes (i.e. 15 minutes prior to the meal). After 30 minutes, a liquid meal (200 ml, 300 kcal, 13% proteins, 48% carbohydrates, 39%, Nutridrink®, Nutricia, Bornem, Belgium) was administered. In all patients gastric tone measurement was continued for 60 minutes after the meal.

Data analysis

Gastric half emptying time ($t_{1/2}$) were calculated from the $^{13}\text{CO}_2$ and $^{14}\text{CO}_2$ excretion curves as previously described (17,18).

The endpoint of the satiety test was the amount of calories ingested until the

occurrence of maximum satiety (score 5) (4,19).

In the gastric barostat studies, for each 2 minute distending period, the intragastric volume was calculated by averaging the recording. Perception threshold was defined as the first level of pressure and the corresponding volume that evoked a perception score of 1 or more. Discomfort threshold was defined as the first level of pressure and the corresponding volume that provoked a score of 5 or more. Hypersensitivity to gastric distention was defined as a discomfort threshold below the mean minus 2 standard deviations in healthy volunteers (<6.6 mm Hg) (4,5). Gastric tone before and after administration of the meal was measured by calculation of the mean balloon volume for consecutive 5 minute intervals. The meal-induced gastric relaxation was quantified as the difference between the average volumes during 30 minutes before and 60 minutes after the administration of the meal. Impaired accommodation to a meal was defined as a meal-induced relaxation below the mean minus 2 standard deviations in healthy volunteers (<64 ml) (4,5).

Statistical analysis

The primary outcome variable was the improvement in DSS scores from baseline. Secondary outcome variables were the effects of treatment on the severity of the 4 individual cardinal dyspepsia symptoms and nausea in the DSS, on solid gastric emptying, on weight and nutrient tolerance and on quality of life scores. The study was powered with 85% sensitivity at $p < 0.05$. The sample size was calculated based on a previous study(20), and the 30% was based on existing regulatory views and recommendations for clinically meaningful benefit in functional disorders(21,22).

RESULTS

Dyspepsia symptom severity and weight evolution

Per protocol analysis

In PP analysis, the drug-by-week interaction effect was borderline significant [$F(2,55)=3.11$, $p=0.053$]. Planned contrasts revealed a significant difference between

week 0 (10.2 ± 0.7) and week 4 (6.8 ± 1.0) as well as week 8 (7.5 ± 1.1) for mirtazapine ($p=0.001$ and $p=0.004$, respectively). For placebo, there were no significant differences between week 0 (11.6 ± 1.1) and week 4 (11.2 ± 1.4) or week 8 (10.5 ± 1.0) ($p=0.67$ and $p=0.38$, respectively). The difference in change from week 0 between mirtazapine and placebo was significant at week 4 (-3.4 ± 0.9 versus -0.4 ± 0.9 , $p=0.049$, Cohen's $d=0.86$) but not at week 8 (-2.7 ± 0.8 versus -1.1 ± 0.8 , $p=0.31$, Cohen's $d=0.52$).

Daily diaries

The weekly average scores for the 3 cardinal FD symptoms available in the diaries (epigastric pain, postprandial fullness, early satiation) as well as nausea are summarized in *Figure 3*. Compared to the run-in period, placebo treatment was associated with significant improvement in nausea ratings at week 2 and week 8. With mirtazapine, compared to the run-in period, significant improvement occurred for severity ratings of early satiation from week 3 onwards, nausea improved from week 2 until week 5 included, and postprandial fullness improved at week 4 only. No significant improvement in pain ratings was found in any of the treatment arms. For early satiation, the drug-by-week interaction effect was borderline significant [$F(8,226)=1.96$, $p=0.052$], indicating a different evolution of early satiation ratings between the two treatment arms (*Supplementary Figure 2*).

